

4-1BB Ligand / CD137 Ligand / TNFSF9

Co-stimulatory genes

Co-stimulatory molecules are membrane-bound molecules which play a crucial role in T cell activation. Abundantly expressed on antigen presenting cells, co-stimulatory molecules provide a secondary signal to antigen-T cell receptor binding by interacting with independent receptors on T cells. This secondary signal is required to induce T cell proliferation and secretion of cytokines. Co-stimulatory molecules have been used in cancer therapies to increase the immunogenicity of tumor cells and elicit antitumoral immune responses to non-immunogenic tumors. Also, vaccination approaches have benefited from the co-transfer of co-stimulatory molecules with antigens.

4-1BBL

4-1BB ligand (4-1BBL) is a membrane protein belonging to the superfamily of tumor necrosis factor (TNF) which provides a co-stimulatory signal to T cells. 4-1BBL is expressed on antigen presenting cells (APCs). 4-1BB, the receptor of 4-1BBL, is present on activated T cells. Interaction between 4-1BB (on T cells) and its ligand (on the APC) increases the activity of both APCs and T cells: APC's proliferation, cell adhesion and/or secretion of various cytokines is elicited, and T cells proliferation is stimulated (Vinay and Kwon, 1998).

Triggering the 4-1BB molecule could provide a treatment for cancer by activating T cells directed against the tumor. Indeed, treatment with antibodies against 4-1BB eradicate established tumors (Melero *et al.*, 1997). Moreover, transduction of 4-1BBL and B7.1 into poorly immunogenic tumor cells induces a systemic antitumoral CTL response (Melero *et al.*, 1998).

	Human Gene	Murine Gene
ORF size	762bp	927bp
Plasmid backbone	pORF	pORF
Subclone with	Ncol - Nhel	BspHI - Nhel

- Martinet O, Ermekova V, Qiao JQ, Sauter B, Mandeli J, Chen L, Chen SH (2000) Immunomodulatory Gene Therapy With Interleukin-12 and 4-1BB Ligand: Long- Term Remission of Liver Metastases in a Mouse Model. *J Natl Cancer Inst* 92(11):931-936
- Vinay, D.S., and Kwon, B.S. Role of 4-1BB in immune responses. *Sem. Immunol.* 10: 481-489.
- Melero, I., Shuford, W.W., Newby, S.A., Aruffo, A., Ledbetter, J.A., Hellstrom, K.E., Mittler, R.S., and Chen, L. (1997). Monoclonal antibodies against the 4-1BB T-cell activation molecule eradicate established tumors. *Nat. Med.* 3: 682-685.
- Melero, I., Bach, N., Hellstrom, K.E., Aruffo, A., Mittler, R.S., and Chen, L. (1998). Amplification of tumor immunity by gene transfer of the co-stimulatory 4-1BB ligand: synergy with the CD28 co-stimulatory pathway. *Eur. J. Immunol.* 28: 1116-1121.

L15 ANSWER 55 OF 56 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:506168 CAPLUS
DOCUMENT NUMBER: 121:106168
TITLE: Comparison of adjuvant activities of aluminum phosphate, calcium phosphate and stearyl tyrosine for tetanus toxoid
AUTHOR(S): Gupta, Rajesh K.; Siber, George R.
CORPORATE SOURCE: Massachusetts Public Health Biol. Lab., State Lab.
Inst., Jamaica Plain, MA, 02130, USA
SOURCE: Biologicals (1994), 22(1), 53-63
CODEN: BILSEC; ISSN: 1045-1056
DOCUMENT TYPE: Journal
LANGUAGE: English
TI Comparison of adjuvant activities of aluminum phosphate, calcium phosphate and stearyl tyrosine for tetanus toxoid
AB The adjuvant activity of three adjuvants, aluminum phosphate (AlPO₄), calcium phosphate (CaHPO₄) and stearyl tyrosine for tetanus toxoid (TT) were compared to sol. TT in mice at a dose of 0.5 Lf (1/10th of the single human dose) and in guinea-pigs at a dose of 7.5 Lf (1.5 times the single human dose). Three TT preps. varying in purity were used: (1) ammonium sulfate ptd. formalin detoxified tetanus toxin (AS-TT); (2) AS-TT ultrafiltered to remove low mol. wt. peptides (UF-TT); and (3) chromatog. purified tetanus toxin subsequently detoxified with formalin (CP-TT). After primary immunization of mice, AlPO₄ adsorbed TTs induced higher toxin-neutralizing and IgG (by ELISA) antibodies than CaHPO₄, stearyl tyrosine adsorbed or sol. TT preps., but this difference was no longer present after secondary immunization. TT preps. of varying purities showed similar antibody responses after primary and secondary immunizations when adsorbed on each adjuvant. CP-TT prep. showed the highest neutralizing antibody level amongst sol. preps. after the first dose. All the preps. induced mainly IgG1 antibodies. However, stearyl tyrosine adsorbed TT induced relatively higher IgG2a and IgG2b responses than AlPO₄, CaHPO₄ adsorbed or sol. TTs particularly after booster injection. No prep. induced detectable IgG3 or IgM antibodies. AlPO₄ adsorbed preps. induced higher IgE antibodies than CaHPO₄ and stearyl tyrosine adsorbed vaccines. Among the sol. preps., CP-TT induced lower anti-TT IgE antibodies than std. AS-TT. All these preps. were also tested in the US potency test for adsorbed TT in guinea-pigs. While all the preps. passed this test, AlPO₄ adsorbed TT prens. induced higher neutralizing and IgG antibodies than CaHPO₄ and stearyl tyrosine adsorbed or sol. TT prens. In these animal models, purified TT was a strong immunogen and traditional AlPO₄ adjuvant gave the highest antibody responses.
L15 ANSWER 56 OF 56 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1979:502174 CAPLUS
DOCUMENT NUMBER: 91:102174
TITLE: Inhibition of cortisone action in mice by heparin
AUTHOR(S): Jokay, I.; Karczag, E.; Kelemenics, K.; Foldes, I.
CORPORATE SOURCE: Microbiol. Res. Group, Hung. Acad. Sci., Budapest, H-1529, Hung.
SOURCE: Endokrinologie (1979), 73(2), 199-208
CODEN: ENDKAC; ISSN: 0013-7251

DOCUMENT TYPE:

Journal

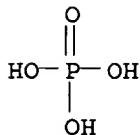
LANGUAGE:

English

AB A single dose of heparin [9005-49-6] applied in a depot-form (Freund's incomplete adjuvant or Ca-phosphate gel) inhibited the effects of i.p. injected cortisone [53-06-5] on the lymphoid organs (thymus and spleen), on the peritoneal and peripheral lymphoid cell count and serum .gamma.-globulin level as well as on liver glycogen deposition in mice. The same dose of heparin did not influence the action of hydrocortisone [50-23-7] measured on thymic and splenic involution and liver glycogen content. The route of cortisone administration seemed to be crit., as heparin showed no or only minor effects when cortisone was given s.c.; moreover, the action of cortisone was more marked by s.c. than by i.p. administration.

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L1 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2003 ACS
 RN 10103-46-5 REGISTRY
 CN Phosphoric acid, calcium salt (8CI, 9CI) (CA INDEX NAME)
 OTHER NAMES:
 CN Calcium phosphate
 CN Crodax DP 30
 CN Dikal 21
 CN Dynafos
 CN E 341
 CN KDV 15u
 CN LF-CP-ZA
 CN Man-Gill 51504
 MF Ca . x H3 O4 P
 CI COM
 LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSNB, DIOGENES, EMBASE, ENCOMPLIT, ENCOMPLIT2, ENCOMPPAT, ENCOMPPAT2, GMELIN*, IFICDB, IFIPAT, IFIUDB, MEDLINE, MSDS-OHS, PDLCOM*, PIRA, PROMT, TOXCENTER, TULSA, USPAT2, USPATFULL
 (*File contains numerically searchable property data)
 Other Sources: EINECS**, NDSL**, TSCA**
 (**Enter CHEMLIST File for up-to-date regulatory information)
 CRN (7664-38-2)

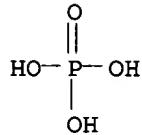


●x Ca

5099 REFERENCES IN FILE CA (1957 TO DATE)
 100 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 5113 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L1 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2003 ACS
 RN 7758-87-4 REGISTRY
 CN Phosphoric acid, calcium salt (2:3) (8CI, 9CI) (CA INDEX NAME)
 OTHER NAMES:
 CN .alpha.-Tricalcium phosphate
 CN .beta.-TCP
 CN .beta.-Tricalcium phosphate
 CN .beta.-Whitlockite
 CN Apamicron AP 12C
 CN Biphasic calcium phosphate
 CN Bonarka
 CN C 13-09SF
 CN Calcium orthophosphate
 CN Calcium orthophosphate (Ca₃(PO₄)₂)
 CN Calcium phosphate
 CN Calcium phosphate (3:2)
 CN Calcium phosphate (Ca₃(PO₄)₂)

CN Calcium tertiary phosphate
CN Cerasorb
CN Ceredex
CN Multifos
CN Ostram
CN Phosphoric acid calcium(2+) salt (2:3)
CN Posture
CN Posture (calcium supplement)
CN Synthograft
CN Synthos
CN TCP
CN TCP 10
CN Tertiary calcium phosphate
CN Tribasic calcium phosphate
CN Tricalcium diphosphate
CN Tricalcium orthophosphate
CN Tricalcium phosphate
CN Tricalcium phosphate (Ca₃(PO₄)₂)
DR 1344-15-6, 123211-19-8
MF Ca . 2/3 H₃ O₄ P
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DETHERM*, DIOGENES, DRUGU, EMBASE, GMELIN*, HSDB*, IFICDB, IFIPAT, IFIUDB, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PDLCOM*, PHAR, PIRA, PROMT, TOXCENTER, TULSA, USPAT2, USPATFULL, VETU, VTB
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
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CRN (7664-38-2)



●3/2 Ca

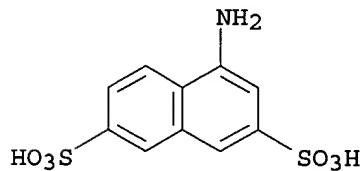
6820 REFERENCES IN FILE CA (1957 TO DATE)
107 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
6834 REFERENCES IN FILE CAPLUS (1957 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
 RN 1306-06-5 REGISTRY
 CN Hydroxylapatite (Ca₅(OH)(PO₄)₃) (9CI) (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN Hydroxylapatite (8CI)
 OTHER NAMES:
 CN Alveograf
 CN AMDRY 6021
 CN Apaceram
 CN APAFILL-G
 CN Apatite
 CN Apatite hydroxide (Ca₁₀(PO₄)₆(OH)₂)
 CN Boneceram P
 CN Bonfil
 CN Calcium hydroxyapatite
 CN Ceratite
 CN Durapatite
 CN FKI
 CN HAP-B
 CN Hy-Apatite
 CN **Hydroxyapatite**
 CN Interpore 200
 CN Interpore 500
 CN Monite
 CN Supertite 10
 CN Synamel
 CN Tri-Tab
 CN Win 40350
 DR 12440-80-1, 136841-77-5, 196875-13-5
 MF Ca . H O . O₄ P
 AF Ca₅ H O₁₃ P₃
 CI MNS, COM, TIS
 LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO,
 CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS,
 CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DRUGU,
 EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS,
 NIOSHTIC, PIRA, PROMT, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL
 (*File contains numerically searchable property data)
 Other Sources: DSL**, EINECS**, TSCA**
 (**Enter CHEMLIST File for up-to-date regulatory information)

Component	Ratio	Component Registry Number
HO	1	14280-30-9
O ₄ P	3	14265-44-2
Ca	5	7440-70-2

12129 REFERENCES IN FILE CA (1957 TO DATE)
 342 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 12164 REFERENCES IN FILE CAPLUS (1957 TO DATE)
 5 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

ER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 6251-07-6 REGISTRY
CN 2,7-Naphthalenedisulfonic acid, 4-amino- (7CI, 8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN 1-Amino-3,6-disulfonaphthalene
CN 1-Aminonaphthalene-3,6-disulfonic acid
CN 1-Naphthylamine-3,6-disulfonic acid
CN 4-Amino-2,7-naphthalenedisulfonic acid
CN **Freund acid**
FS 3D CONCORD
MF C10 H9 N O6 S2
CI COM
LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS, CHEMCATS, CHEMLIST, IFICDB,
IFIPAT, IFIUDB, SPECINFO, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

54 REFERENCES IN FILE CA (1957 TO DATE)
54 REFERENCES IN FILE CAPLUS (1957 TO DATE)